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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,820	01/06/2006	Lars Winther	09138.0045	3909

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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,820	WINTHER ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-116* is/are pending in the application.

4a) Of the above claim(s) *91,93,94 and 105-116* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-90,92 and 95-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 5/4/2009, is acknowledged and has been entered. Claim 88 was amended. Claims 88-116 are pending in the application, with claims 91, 93-94, and 105-116 currently withdrawn. Claims 88-90, 92, and 95-104 are subject to examination below.

Objections/ Rejections Withdrawn

2. The rejection of claim 88 under § 112, 2nd paragraph has been withdrawn in response to Applicant's amendment to the claim.

3. The rejections of claims 88-90, 92, 95-96, and 98-103 are rejected under § 102(b) as being anticipated by Battifora et al.; of claim 97 under § 103(a) as being unpatentable over Battifora et al. in view of Lodish et al.; and of claim 104 under § 103(a) as being unpatentable over Battifora et al. in view of O'Leary et al.; have been withdrawn in response to Applicant's amendments to claim 88 to recite that the compact particle does not express the detectable entity.

Priority

4. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/IB04/02682, filed 7/8/2004, which claims priority under 35 U.S.C. 119(e) from provisional application No. 60/486,381, filed 7/11/2003. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. GB 0315991.0, filed on 7/8/2003 in Great Britain.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 88, 92, 95-96, 98-100, and 102-104 are rejected under 35 U.S.C. 102(b) as being anticipated by Cosgrove et al. (EP 0 345 953 A2, Applicant's Information Disclosure Statement of 3/22/2006).

Cosgrove et al. teach a standard for use as a positive quantitative control (i.e., reference standard) comprising pellets of an absorbent gel (i.e., compact particles), where specific concentrations of an antigen of interest are adsorbed and confined in the pellets (i.e., comprising a quantity of detectable entity attached to the compact particle). See in particular the abstract; column 2, lines 15-39; and column 4, line 54 to column 6, line 4. For example, the antigen may be immobilized within the pellets by fixation (column 5, lines 39-48; and column 7, lines 17-24). Cosgrove et al. further teach that the pellets may be embedded into a gel block (i.e., support medium; see column 6, lines 5-23; column 7, lines 24-57). As the pellets are made up of gel, they do not naturally express antigen and must be exposed to solutions containing antigen (see column 7).

With respect to claim 92, Cosgrove et al. indicate that the antigen of interest (i.e., detectable entity) is detected by immunocytochemical staining alongside staining of tissue specimens for diagnostic purposes (abstract and column 1, lines 1-4). From this, it would be at

once envisaged that the antigen of interest is derived from tissue and would be indicative of a disease or condition.

With respect to claims 95-96, Cosgrove et al. teach that the pellets may be embedded in the gel block in a lattice array, for example individual wells (see column 4, lines 1-9; column 6, lines 25-34; column 7, lines 24-39; Figures 1-2; and claim 15). As the detectable entity is present within the pellets, this means that the detectable entity is also present in defined regions of the array (e.g., wells). The gel block may be sectioned using a microtome to provide a thin section that will incorporate regions corresponding with the various embedded pellets, i.e. a cross-section (see column 6, lines 9-22; column 7, lines 54-58; and column 8, lines 37-45).

With respect to claim 100, the antigen can be detected by immunocytochemical staining, e.g. us9ing an antibody (see especially at column 6, lines 16-22 and at column 8, lines 13-45).

With respect to claims 102-103, the reference standard may contain pellets of different antigen concentrations contained in different wells (column 7, lines 11-39 and Figure 2).

With respect to claim 104, pellets having no antigenic material can be included in the gel block to serve as controls (column 5, lines 54-56).

7. Claim 97 is rejected under 35 U.S.C. 102(b) as being anticipated by Cosgrove et al. in light of the evidence of Hood et al. ("Unravelling the proteome of formalin-fixed paraffin-embedded tissue" Briefings in Functional Genomics and Proteomics 2006 5(2):169-175).

Cosgrove et al. is as discussed in detail above, which teaches immobilization of antigen within the pellets (compact particles) by fixation, such as via formalin (column 5, lines 39-48; and column 7, lines 17-24). Hood et al. provide evidence that the process of formalin fixation

results in various combinations of intra- and inter-molecular covalent crosslinks between proteins, RNA and DNA (page 170, left column, first paragraph).

Therefore, the teachings of Cosgrove et al. in which the antigen is immobilized by formalin fixation anticipate the claimed invention since this process involves covalent attachment, as evidenced by Hood et al.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 88-90, 92, and 95-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Battifora et al. (U.S. 5,610,022) in view of Edge (U.S. 2002/0127205 A1).

Battifora et al. teach an internal control or standard for quantitative assay by immunohistochemistry of target molecules (i.e., reference standard for a detectable entity),

comprising cells (i.e., compact particles) that express a known amount of a target molecule, such as estrogen or progesterone receptors (i.e., detectable entities). The instant specification defines the term "attached" so as to encompass any association between the detectable entity and the compact particle, e.g. intracellular detectable entities (see page 64, lines 1-14 and page 52), such that the target molecules expressed by cells as in Battifora et al. would be considered to be "attached" to the cells. The cells are embedded in a gel (i.e., support medium). See in particular the abstract; column 1, lines 51-56; column 2, lines 10-24; column 3, line 12 to column 4, line 15; and Examples I-II.

The teachings of Battifora et al. differ from the claimed invention in that the reference teaches that the cells expressing known amounts of antigen are preferably obtained by transfection with a gene encoding for the desired molecule or antigen, i.e. the cells express the antigen. As such, the reference does not specifically teach a reference standard in which the compact particles do not express the detectable entity.

Edge teaches various methods by which cells may be made to express antigens (in this case, immunoregulatory molecules). See [0075]-[0100]. In particular, Edge teaches that genetic material encoding the antigens may be introduced into cells [0077]-[0078]. Other methods of modifying cells to express antigens include coupling the antigens to the cell, preferably to the surface of the cell ([0096] and [0099]). For example, a protein can be chemically crosslinked to a cell surface using commercially available crosslinking reagents [0099].

It is noted that for the purposes of examination of the instant claims the term "express" has been interpreted in light of the specification, in which cells that that "express" are those that produce detectable entity via expression of a gene for the detectable entity, either naturally or by

recombinant gene expression (see especially [0232] and [0261] of the published application). By contrast, cells that "do not express" detectable entity are those that have been made to be attached to it by chemical coupling.

Therefore, although Edge employs the terminology "express" in the context of both genetic expression as well as crosslinked cells, the chemically crosslinked cells taught by Edge would not be considered to "express" antigen when this term is read in light of the specification.

In view of the teachings of Edge that cells can be made to "express" antigens either by introducing genetic material encoding the antigens into cells, or alternatively by chemically crosslinking antigens the surfaces of cells, it would have been obvious to one of ordinary skill in the art to produce the cells having known amounts of antigen of Battifora et al. by chemically crosslinking antigens to the surfaces of cells, rather than by introducing genetic material. One would be motivated to do this because the teachings of Edge establish that both methods were recognized in the art to be suitable for the same purpose, namely for producing cells that contain an antigen of interest. As such, one of ordinary skill in the art would have had a reasonable expectation of success in substituting chemical crosslinking for genetic engineering in order to obtain cells that contain known amounts of antigen.

In addition, because Edge indicates that chemical coupling can be used to attach antigens to the surfaces of cells, one would also be motivated to employ this method when conducting quantitative immunohistochemistry methods upon antigens of interest that are cell surface antigens. As Battifora et al. clearly teach that their invention can be applied to any desired molecules (see column 3), one would also have had a reasonable expectation of success in this regard.

With respect to claim 92, Battifora et al. teach that the target molecules may be indicative of an abnormal condition (column 1, lines 23-27).

With respect to claims 95-96, Battifora et al. teach that the target molecules were detected in slices or cross-sections (i.e., defined regions). See Example 1.

With respect to claim 97, Edge teaches chemical crosslinking, i.e. covalent attachment [0099]. Therefore, when employing the crosslinking methods of Edge to produce the cells containing known amounts of antigen of Battifora et al., it would necessarily follow that antigen would be covalently attached to the cells.

With respect to claim 100, the presence of the target molecules may be revealed by binding to specific antibodies (see, e.g., column 14, lines 31-32 and 52-53).

With respect to claim 101, the embedding medium has a box shape as the mold containing the gel is rectangular (Figures 1-2 and column 2, lines 10-24).

With respect to claims 102-103, the reference standard may comprise a plurality of layers each comprising different known amounts of the antigen (column 2, lines 3-7 and 14-24). Since the same cells and the same antigens are involved, but that the amount of antigen is varied among layers, this would mean that the density of the antigen is different in different layers.

11. Claim 104 is rejected under 35 U.S.C. 103(a) as being unpatentable over Battifora et al. in view of Edge as applied to claim 103 above, and further in view of O'Leary et al. ("Standardization in immunohistochemistry", Appl Immunohistochem Mol Morphol. 2001 Mar;9(1):3-8).

Battifora et al. and Edge are as discussed in detail above, which teach a reference standard substantially as claimed, but which fails to specifically teach the inclusion of a positive control that comprises a compact particle with substantially no detectable entity. However, it is noted that Battifora et al. does teach a reference standard containing different amounts of antigen (see column 2).

O'Leary et al. relates to standardization of immunohistochemical analysis, and teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible (page 5, last paragraph). Negative controls comprise tissues or cells that do not contain the antigen to be detected (Table 5).

Therefore, it would have been further obvious to include cells that do not contain the target molecule/ antigen to be detected (i.e., detectable entity) as negative controls as taught by O'Leary et al. in the reference standard of Battifora et al. and Edge. One would be motivated to do this in order to allow for standardization of immunohistochemical analyses in which the reference standard is used, based on the explicit teachings by O'Leary et al. that such negative controls should be included whenever possible in immunohistochemistry (which is the analysis method for which the reference standard of Battifora et al. is designed).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 88-90, 92, and 95-104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-32 and 35-41 of copending Application No. 10/547,033 in view of Battifora et al. and Edge.

The claims of Application No. 10/547,033 recite a reference standard comprising (i) a support medium; and (ii) a quantity of at least one detectable entity supported by the support medium (see, e.g., claims 1, 36, and 40).

The claims of Application No. 10/547,033 differ from instant claim 1 in that the copending application does not recite that the detectable entity is attached to a compact particle (such as a cell) that does not express the detectable entity.

Battifora et al. (discussed in detail above) teaches reference standards that include detectable entity provided in the context of cells (i.e., compact particles) that contain a known amount of the detectable entity (target molecule). The cells are embedded in a gel (i.e., support medium) so as to produce pseudo tissue. See in particular the abstract; column 1, lines 51-56; column 2, lines 10-24; column 3, line 12 to column 4, line 15; and Examples I-II.

Although Battifora et al. exemplify producing the cells by transfection with a gene encoding for the desired molecule or antigen (i.e., such that the cells "express" the antigen as this term is used according to the instant specification), the teachings of Edge (discussed in detail above) establish it was known that cells can be made to bear antigens either by this process or alternatively by chemically crosslinking antigens to the surfaces of cells.

When taken together, it would have been obvious to one of ordinary skill in the art to provide the detectable entities in the reference standard of Application No. 10/547,033 in the context of cells containing the detectable entities, and to embed such cells in the support medium as taught by Battifora et al. Furthermore, it would have been obvious to substitute chemical crosslinking (as taught by Edge) for genetic engineering as a known means of obtaining cells that have an antigen of interest. One of ordinary skill in the art would have recognized that combination of the prior art elements in this manner according to known methods would have performed the same function, namely to obtain cells having known amounts of antigen for use as a reference standard.

With respect to claims 103-104, Application No. 10/547,033 recites a reference standard containing areas at different densities, including areas with no detectable entity (see claims 57-58).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

14. Applicant's arguments with respect to claims 88-90, 92, and 95-104 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chang (U.S. 4,433,059) also teaches that antigens cells can be chemically attached to the surfaces of cells (column 2, lines 3-16).

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641